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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/465,802	12/17/99	GARCIA-BLANCO	M 1579-321

EXAMINER

HM12/0328

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/465,802	Applicant(s) Garcia-Blanco And Carstens
	Examiner Jennifer Hunt	Group Art Unit 1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-4* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

1. It is noted that the specification contains numerous numerical citations, wherein a cited document is cited by a numeral, however there is not accompanying list which states what the reference numbers refer to. Thus numerous citations through the specification, particularly in the examples, fail to refer to the appropriate prior art documents.

Claim Rejections - 35 U.S.C. § 112

2. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 are unclear in the recitation of "metastatic potential", and "increase in metastatic potential". The metes and bounds of metastatic potential cannot be determined. It is not clear how such "potential" would be determined or measured. The qualities and properties encompassed by "metastatic potential" are never clearly set forth in the specification or claims. Further it is not possible how an increase in metastatic potential would be determined or measured. Specifically, it is not clear what level said increase is determined from (ie: increased above what?)

Claims 1-4 are unclear in the recitation of "predominant expression". The metes and bounds of "predominant expression" cannot be determined. It is not clear what would be considered predominant expression and what would not. Specifically, it is not clear at what point of difference would expression of one isoform over another be considered "predominant".

3. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determination of prostate malignancy or androgen resistance in a rat patient or human cell line by assaying mRNA, does not reasonably provide enablement for determination of metastatic potential in patients including humans, or determination of metastatic potential by assaying the presence of the isoforms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The specification teaches measurement of FGF-R2 IIIb and IIIc isoform mRNA in 2 specific cell lines and subsequent determination, based solely on the properties of those cell lines that the expression of FGF-R2 IIIc is correlative to increased likelihood of malignancy and

androgen resistance. The specification also teaches production of antibodies to the FGF-R2 IIIb and IIIc isoform. The specification does not teach detection of the FGF-R2 IIIb and IIIc isoforms themselves, or detection of the FGF-R2 IIIb and IIIc isoforms using antibodies.

The claims are broadly drawn to determination of metastatic potential in any prostate cancer patient by measuring FGF-R2 IIIb and IIIc isoform mRNA or the isoforms themselves.

Those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be over expressed in CHO cells following exposure to radiation, without any concomitant over expression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia,

said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Thus one of skill in the art would not be able to determine metastatic potential of a prostate cell by measuring the isoforms using an antibody. Only mRNA methods are enabled. Any further extrapolation is an invitation to experiment, with correlation to diagnosis lacking as set forth above.

Further, it is also well established in the art that conclusions drawn in cell lines cannot easily be extended to human patients. Those of skill in the art recognize that in vitro assays are generally useful to screen the effects of agents on target cells. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo experiment as compared to the very narrowly defined and controlled conditions of an in vitro assay does not permit a single extrapolation of in vitro assays to human activity with any reasonable degree of predictability. Cancer is by it's very nature unpredictable, because it is the result of one or more of any number of alterations in normal cellular physiology. Further, in vitro cell lines are artificially generated models, conclusions from which cannot blindly be extended to human patients. Activity of a cancer cell line is not necessarily reflective of the actual in vivo activity of that type of cancer.

Therefor, for the reasons set forth above, one of skill in the art would not be enabled to practice the full scope of the invention as claimed.

Claim Rejections - 35 U.S.C. § 102

4. Claims 1-3 are rejected under 35 U.S.C. 102(a) as being anticipated by Carstens et al., Oncogene Vol. 15, pages 3059-3065, December 18, 1997.

Carstens et al. teaches a method of determining the increased metastatic potential (likelihood of malignancy and androgen resistance) of a prostate tumor in a patient (a mouse) by assaying for increased expression of the FGF-R2 IIIc isoform over the FGF-R2 IIIb isoform. The assay used measures mRNA transcripts. (See for example, abstract, and pages 3063-3064)

5. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Yan et al., Molecular and Cellular Biology, Vol. 13, No. 8, pages 4513-4522, August, 1993.

Yan et al. teaches a method of determining the increased metastatic potential (likelihood of malignancy and androgen resistance) of a prostate tumor in a patient (a rat) by assaying for increased expression of the FGF-R2 IIIc isoform over the FGF-R2 IIIb isoform. The assay used measures mRNA transcripts. (See for example, abstract, and pages 4514 and 4517)

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

March 24, 2001

Brenda Brumback

BRENDA BRUMBACK
PATENT EXAMINER